REVIEW ARTICLES

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Vitamin D_2 versus vitamin D_3 as a risk factor in compromised bone health

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Abstract

Background: Vitamin D plays an important role in the prevention of many diseases. More than 1 billion people worldwide suffer from vitamin D deficiency. Vitamin D deficiency can contribute to the development of 16 types of cancer (breast, colon, prostate, etc.), cardiovascular diseases, stroke, autoimmune diseases, periodontal pathologies, transplant failure in endo-alveolar surgery, etc. There are several risk factors that would prevent the achievement of treatment objectives. The national protocol for deficiency rickets prevention privileges vitamin D_2 versus vitamin D_3, which creates a medical risk factor compromising oral health in both children and adults. The article provides sufficient arguments in favour of vitamin D_3 vs vitamin D_2 prescription for prophylactic and treatment purposes.

Conclusions: Considering that vitamin D deficiency is currently a global public health problem, it can be proposed to declare vitamin D deficit/deficiency a priority public health problem at the national level. Vitamin D_3 should be elective in preventing deficit. Taking into account the multitude of acute and chronic diseases related to vitamin D deficiency, in order to improve the status of vitamin D in all population categories, it is necessary to include vitamin D_3 in the list of molecules fully subsidized by the state and distributed free of charge at least to children under the age of 5 years and adolescents in the period of intensive growth.

Key words: Vitamin D deficiency, osteoporosis, risk factor, oral health, rickets.

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Introduction

Vitamin D deficiency is a public health problem, affecting more than a billion children and adults worldwide [1]. There is a strong correlation between vitamin D deficiency and a range of acute and chronic diseases and conditions, such as hypocalcemia in newborns, rickets/osteomalacia in children and adolescents, obesity, osteoporosis, type 1 diabetes, asthma, juvenile arthritis, high blood pressure, premenstrual syndrome in teenage girls, depression, fibromyalgia, chronic asthenia syndrome, schizophrenia, neuro-degenerative diseases, including Alzheimer's disease, sarcopenia in adults. Vitamin D deficiency can contribute to the development of 16 types of cancer (breast, colon, prostate, etc.), cardiovascular diseases, stroke, autoimmune diseases, periodontal pathologies, transplant failure in endo-alveolar surgery, etc.

Analysis and discussion

Studies on the role and involvement of vitamin D in oral health are still too few and too recent, but some leads are emerging. Thus, hypovitaminosis D would be correlated with a higher risk of periodontitis particularly through an overexpression of RANK L, responsible for osteoclastogenesis [2, 3], also leading to a decrease in bone density [4]. The deficiency would also increase the rate of dental loss, again in correlation with bone metabolism [5] but also through a lower resistance to infection.

The link between caries risk in children and serum vitamin D levels has been demonstrated in some studies, but the results are still conflicting [6-8]. On the other hand, its role in MIH (Molar – Incisor – Hypomineralization) has been statistically demonstrated [9]. In terms of implantology, vitamin D is gradually emerging as a factor

favoring good osseointegration, administered systemically [10, 11] or topically [12], as well as a better defense against infections, especially during bone grafting.

For a successful promotion of national strategies for vitamin D deficiency correction, it is necessary to identify and prevent the risk factors that lead to the high maintenance of its metabolism disturbance. The number of risk factors for hypovitaminosis D varies from country to country. Their identification and correction would allow a much more effective prophylaxis of rickets and other conditions related to vitamin D deficiency, since its deficiency begins during pregnancy and is associated with a significant reduction in bone mineral density, which persists until the age of 9-10 years after birth and even until adulthood if it is not corrected in time [13]. The risks of developing a vitamin D deficiency are found in all corners of the world, regardless of the socio-economic level of the countries. Thus, official statistics from Africa, Australia, the Far East, Mongolia, New Zealand, Brazil, have documented a continuous increase in risk factors for vitamin D deficiency in both children and adults [14-16].

Putting aside the publications of the last 5 years from France, Canada and the USA, on the need to review the prophylactic doses used in vitamin D deficiency to increase them for all population categories that aim not only to strengthen bone health, but also extraosseous health (oral health, improvement of prognosis after surgery in endo-alveolar procedures, prophylaxis of 16 types of cancer, strengthening the immune and nutritional status, decreasing the incidence and prevalence of cardiovascular, rheumatic, renal, gastrointestinal, dermatological, neurological, neuro-psychological diseases, etc.), it is important to point out that in the national protocol for the prevention of deficiency rickets of the Ministry of Health, Labor and Social Protection No 105 of 04.06.2010, vitamins D_2 and D_3 are considered equivalent both in terms of dosage and action. The research in recent years has eloquently demonstrated that these vitamins, having different origins, are also very different in terms of effectiveness on the human body and phosphocalcic metabolism [11-13, 17-21], almost unanimously giving priority to vitamin D_3.

Thus, numerous randomized studies or meta-analysis have demonstrated that the use of Vitamin D_3 is still more effective in increasing the serum level of 25(OH)D3, compared to the administration of the same dose of Vit D2, especially in long-term treatment duration [22-24].

Vitamins D_2 and D_3 work as prohormones, therefore, do not have independent biological effects, a series of biochemical transformations in the human body being required for them to manifest the effect. These 2 molecules are of different origin – Vitamin D_2 – of vegetable origin, vitamin D_3 – of animal origin, differing at the biochemical level by the structure of the lateral chains, but having the sterol ring in common. To become active, both substances need two successive hydroxylations – the first in the liver – under the influence of 25-hydroxylase (with the involvement of microsomal cytochrome P450 2R1 and mitochondrial cytochrome P450 27A1), resulting in 25-hydroxyvitamin D (calcidiol). In the kidneys, a second hydroxylation occurs under the influence of the enzyme 1-alphahydroxylase (cytochrome P450 B1), resulting in 1,25-dihydroxyvitamin D_2/D_3. Hydroxylations are controlled by the level of parathormone, through homeostatic mechanisms. Although both vitamins eventually reach the active form of calcitriol, statistical data show that taking D_3 results in a more pronounced increase in 25(OH)D levels compared to D_2.

Scientists have established that vitamins D_2 and D_3 have different affinities for the vitamin D receptor (VDR), which in turn activates 24-hydroxylase – the enzyme responsible for the inactive metabolite calcitriol formation. Moreover, vitamin D_2 is inactivated faster by this enzyme than vitamin D_3, so it has a shorter half-life than vitamin D_3. It was found that 24(R),25-dihydroxyergocalciferol ($24,25\text{-}(OH)_2D_2$) has 1.7 times weaker affinity than 24(R),25 dihydroxycholecalciferol ($24,25\text{-}(OH)_2D_3$), the latter also having a much higher affinity to the plasma transport protein of vitamin D – DBP – resulting in a half-life 1.3 times longer than $1,25\text{-}(OH)_2D_2$ vis-à-vis VDR in the intestine. Scientists claim that this plays an important role in the difference in the action of vitamins D_2 and D_3. It should be noted that $1,24,25(OH)_2D_3$ is also an inactivated product, but already of cholecalciferol. Unlike $1,24,25(OH)_3D_2$, it maintains its affinity for VDR and requires one more oxidation to become completely inactive. Therefore, this additional step gives cholecalciferol (vitamin D_3) an increased potential for biological activity and maintenance of an adequate 25(OH)D status in the body [19, 25]. Vitamin D_3 is assumed to be the "preferred" substrate for the liver 25-hydroxylase, which in combination with the difference in VDR affinity of vitamins D_3 and D_2 and inactivation rate, respectively, only reinforces the importance of using vitamin D_3 prophylaxis.

According to a review by Houghton and Vieth in 2006 [24], the metabolic differences between vitamins D_2 and D_3 are due to the difference in the internal chain structure of the vitamins. Thus, ergocalciferol (vitamin D_2) still has a methyl group in position 24, which slows down the rate of conversion to 25(OH)D and respectively decreases the affinity towards the vitamin D binding protein (DBP). Armas et al. and Heaney et al. demonstrated that vitamin D_3 induces a faster and longer response in maintaining serum 25(OH)D levels. They also demonstrated that after a single bolus administration of 50000 IU of ergocalciferol (vit D_2), $25(OH)D_2$ values decrease much faster (on the 14th day) compared to $25(OH)D_3$ at the same dose of cholecalciferol (elevated values are maintained even on the 28th day) [19, 25]. Thus, 50 000 IU of D_3 and D_2 respectively were used in 2 distinct groups for 12 weeks. The values of the 25(OH)D growth curve were higher for $25(OH)D_3$ than for $25(OH)D_2$. Additionally, it was determined that 6 weeks after finishing the administration of bolus vitamins,

the degradation rate of serum 25(OH)D_2 was higher than for 25(OH)D_3, respectively the concentration of the latter being higher in the serum, and of ergocalciferol decreasing to the initial base values.

Therefore, the most plausible explanation for the better effect of vitamin D_3 supplementation is: a) the increased affinity of vitamin D_3 and its metabolites to VDR, DBP and liver 25-hydroxylase; b) the lack of liver's ability to directly hydroxylate position 24 of the internal chain of vit D_3 as opposed to vit D_2.

A 2011 Cochrane study highlighted the significant differences between the two vitamins and the death rate examined for people who supplemented their diet with vitamin D_2 compared to those who did so with vitamin D_3. Analysis of 50 randomized controlled trials, which included nearly 100000 participants, showed a relative risk reduction of 6% among those who used D_3 and an increase in relative risk of 2% among those who used D_2.

According to recent research, vitamin D_3 is about 85% better at increasing and maintaining vitamin D concentrations in the body and produces a storage of vitamin D 200-300% higher than vitamin D_2. It is repeatedly mentioned that any form needs to be converted by the body into a more active form, and vitamin D_3 is converted 500% faster than vitamin D_2. The latter has a shorter deposit life and binds poorly to blood proteins, further hindering their effectiveness.

Moreover, synthetic vitamin D_3 is produced as analog of the natural one by obtaining 7- dehydrocholesterol from cholesterol and then by UV irradiation it turns into D_3. Vitamin D_2, however, is synthesized from ergosterol which is obtained chemically from ergot extracted from molds (fungi). Thus, vitamin D_2, in addition to low biological activity, also has instability to temperature differences, humidity or even dependent on storage containers. Contrary to this, vitamin D_3 is stable. The instability and low purity of vitamin D_2 may also favor higher toxicity compared to D_3, which is more stable and much more purified [24].

Vitamin D_3 increases the total and free 25(OH)D level more than D_2 (25(OH)D concentration increases practically twice faster per week for vitamin D_3 versus vitamin D_2. Finally, another argument in favor of vitamin D_3 is that laboratories do not have kits to determine 25(OH)D_2, which can lead to errors in assessing the status of vitamin D in the body.

In conclusion it can be supposed that the determination of vitamin D status may also be necessary pre-operatively, pre-implant or before any bone grafting.

As several studies have shown, age should not be taken into account, as even young people and children can be deficient.

The elderly population is considered to be deficient, but a preliminary assessment of vit D status would enable better tailoring of supplementation.

Prevention in the field of oral health should be based on more frequent dosing of vitamin D: such test could be considered by its importance as equivalent to taking blood pressure when examined by a physician.

The elements that suggest a deficiency:

– Population groups: elderly, obese, pregnant women
– Clinical: nonspecific diffuse musculoskeletal pain; spontaneous fractures; chronic kidney disease; chronic generalized fatigue; alcoholism and smoking, depression
– Radiological: Decreased bone density
– Biological: increased parathyroid hormone (PTH), hypocalcemia.

Conclusions

Based on the above, the following course of action is proposed:

1. Daily intake of vitamin D is on average 2000 to 4000 IU [25]. The daily intake will therefore have to compensate for the latter.

2. In a healthy population, classical supplementation is around 800 to 1200 IU/day without any risk of toxicity, or 50000 IU/month [25]. People at risk should logically receive a higher dose.

Supplementation can be done in several ways:

- Droplets (Uvedose) 1 million IU percent: 6 to 12 drops per day
- Vials (Uvedose) 100000 IU, 3 to 4 times a year
- Tablets (200, 400, 800 or 1000 IU per tablet depending on the deficiency, 1 tablet per day).

3. For an attack treatment (stoss method), supplementation is done in 2 to 4 doses of 100000 IU, 15 days apart, depending on the severity of hypovitaminosis D.

4. There is a proposal that the currently existing national protocol on deficiency rickets be adapted according to the presented information, favoring the fractional or stoss prescription of vitamin D_3.

5. Based on the fact that vitamin D deficiency is currently a global public health problem, it is necessary to declare the deficit/deficiency of vitamin D as a priority public health problem at the national level.

6. Taking into account the multitude of acute and chronic diseases related to vitamin D deficiency, in order to improve the status of vitamin D in all population categories, it would be useful to include vitamin D_3 in the list of molecules fully subsidized by the state and distributed free of charge at least to children under the age of 5 years and adolescents in the period of intensive growth.

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Authors' contributions

CV designed the study and wrote the manuscript; AR collected the data; AV revised the manuscript critically; EKK collected and carried out the analysis of the literary sources; JFDS collected and conducted the analyses of the literary sources; SJA collected and effected the analysis of the literary sources. All the authors revised and approved the final version of the manuscript.

Ethics approval and consent to participate

No approval was required for this study.

Conflict of interests

The authors have no conflict of interests to declare.